

REMARKS

Claims 1 to 6 and 8 to 20 are pending in the application. Claims 1 to 6 have been withdrawn from consideration as drawn to non-elected subject matter. No claims have been amended or canceled, and no new claims have been added, herein.

Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 8 to 20 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over published PCT application number WO 91/01143 (“the Pillai application”) in view of U.S. Patent number 5,286,847 (“the Gehrke patent”) and Beissert, *et al.*, *J. Investigative Derm.* 1998, 111, 609-615 (“the Beissert article”). Applicants respectfully traverse the rejection because the Office has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002). In addition, the Patent Office must demonstrate that the proposed modification or combination of the prior art would have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Applicants respectfully submit that the Office has failed to provide credible evidence of a suggestion or incentive that would have motivated those of ordinary skill in the art to combine the teachings of the cited references. The teachings of the Gehrke patent, in fact, would have led those skilled in the art away from combining the patent’s teachings with those of the Pillai application and the Beissert article.

The Pillai application describes methods of administering a vaccine composition comprising a mixture of an antigen and an interleukin absorbed onto a mineral in suspension to an animal (page 6, lines 4 to 8). The interleukins that can be used in the composition are

said to include interleukin-1 α (“IL-1 α ”) and interleukin-1 β (“IL-1 β ”) (page 2, lines 10-11). The application fails to teach or suggest, however, methods that comprise administering *an interleukin-1 mutein having reduced toxicity* in combination with a vaccine antigen.

The Gehrke patent describes a mutant precursor IL-1 β polypeptide in which the arginine at position 127 of the polypeptide is replaced with glycine (“IL-1 β _{Arg127-Gly} mutant”), and describes experiments in which the biological activity and receptor binding activity of the mutant were characterized. The patent reports that the IL-1 β _{Arg127-Gly} mutant exhibited decreased biological activity as compared to native, mature IL-1 β polypeptide in a thymocyte costimulation assay (Figure 2), and further reports that the IL-1 β _{Arg127-Gly} mutant bound the IL-1 receptor as efficiently as the native, mature IL-1 β polypeptide (Figure 3). The patent further states that the mutant can act as an IL-1 β inhibitor by binding to IL-1 receptors and interfering with the binding of native IL-1 β (col. 3, lns 55 to 59). The patent explains that the mutant can thus be used as an “anti-inflammatory, *anti-immune agent*” for the treatment of autoimmune diseases caused by the excessive or unregulated action of IL-1, such as rheumatoid arthritis, osteoarthritis, and gouty arthritis (col 4, lns 27 to 31 and lns 39 to 45)(emphasis added). The Gehrke patent fails, however, to teach or suggest that the IL-1 β _{Arg127-Gly} mutant possesses *immunostimulatory* or *immunoenhancing* activity that would make the mutant useful as a vaccine adjuvant. In fact, the patent teaches away from the use of the mutant as an adjuvant by teaching its use as an *anti-immune agent*.

The Beissert article describes the treatment of Langerhans cell-enriched epidermal cells with either IL-1 α or IL-1 β . The treated cells were pulsed with S1509a tumor-associated antigens and then used to immunize mice (abstract). Epidermal cells treated with 100 U IL-1 β per ml were able to induce protective tumor immunity, but epidermal cells treated with either 100 U IL-1 α or 1000 U IL-1 β failed to confer protective immunity (abstract). The article fails to teach or suggest using an IL-1 α or IL-1 β mutein having reduced toxicity as a vaccine adjuvant, however.

Those skilled in the art would not have been motivated to combine the teachings of the Gehrke patent, the Pillai application, and the Beissert article because the Gehrke patent teaches away from its combination with the other two references. Specifically, the Gehrke patent teaches that the IL-1 β _{Arg127-Gly} mutant exhibited reduced biological activity relative to

native IL-1 β , but fails to teach or suggest that the mutant possesses immunostimulatory and immunoenhancing activities comparable to those of native IL-1 β . Those skilled in the art would not have expected the IL-1 $\beta_{\text{Arg127-Gly}}$ mutant to possess such immunostimulatory properties based upon the reference's teaching that the mutant is useful as an *anti-immune agent*. Those skilled in the art, therefore, would not have reasonably believed that the IL-1 $\beta_{\text{Arg127-Gly}}$ mutant described in the Gehrke patent would have been useful as a vaccine adjuvant, and, accordingly, would not have been motivated to combine the teachings of the Gehrke patent with those of the Pillai application and the Beissert article. Moreover, those skilled in the art would not have had a reasonable expectation of success for the combination due to the lack of any suggestion in the references that the IL-1 $\beta_{\text{Arg127-Gly}}$ mutant possesses immunostimulatory and immunoenhancing activities.

Although the Office Action asserts that "one would be motivated to modify the method [of the Pillai application] to use the IL-1 β mutant [of the Gehrke patent] which has high receptor binding affinity but significantly reduced activity,"¹ as previously discussed, the Gehrke patent, the Pillai application, and the Beissert article, when considered individually or in combination, fail to teach or suggest that the IL-1 $\beta_{\text{Arg127-Gly}}$ mutant possesses immunostimulatory and immunoenhancing activities that would make the mutant useful as a vaccine adjuvant, and the Gehrke patent actually teaches away from using the mutant for such a purpose. Absent a teaching or suggestion that the IL-1 β mutant possesses immunoenhancing and immunostimulatory activities, those skilled in the art would not have reasonably expected that the mutant would have been useful as a vaccine adjuvant. Those skilled in the art would therefore not have been motivated to combine the teachings of the Gehrke patent with those of the Pillai application and the Beissert article. The Office Action has failed to offer any credible evidence to the contrary and has, therefore, failed to establish *prima facie* obviousness. Applicants, accordingly, respectfully request withdrawal of the rejection.

¹ Office action dated June 1, 2006, page 4.

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Information Disclosure Statement

Applicants note that references 1 to 31 were crossed through and not initialed on the Form PTO 1449 that was originally filed November 19, 2003 and that was returned to Applicants' representative with the official action dated June 1, 2006. The Examiner indicated in a telephone conversation that occurred on November 20, 2006 with Ms. Heather Kite that the Form PTO 1449 was not initialed because references 1 to 31 were not submitted to the Patent Office when the accompanying information disclosure statement was filed. According to 37 C.F.R. § 1.98(d) however, Applicants of a continuation application are not required to submit copies of references with an information disclosure statement if the references were submitted in connection with prosecution of the parent application. Applicants of this continuation application are thus not required to submit copies of references 1 to 31 in order to have the references considered by the Patent Office because copies of the references were submitted during prosecution of the parent application. Applicants accordingly, respectfully ask the Office to return an initialed copy of the Form 1449 to Applicants confirming consideration of references 1 to 31.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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